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STUDIES OF CIRCULATORY AND METABOLIC CHANGES DURING
KETAMINE NARCOSIS(U) FOREIGN TECHNOLOGY DIV
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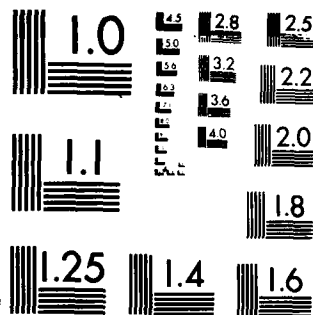
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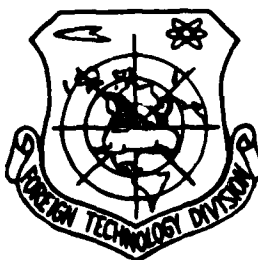
By

I. Hensel, U. Braun, et al.

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STUDIES OF CIRCULATORY AND METABOLIC CHANGES DURING KETAMINE NARCOSIS* **

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Summary

Summary of the main results of the study

Ketamine is used as a representative of the so-called dissociative anesthetics. Its effects on circulation and metabolism were studied in a representative individual test. The results show that ketamine has a stimulating effect on circulation and metabolism. The heart frequency (HF) increases, the heart rate (HZV) increases, the coronary blood supply (V_{cor}) increases, and the myocardial O₂ consumption increases. Together with a reduction in coronary venous saturation.

Among commonly used anesthetics, ketamine obviously occupies an unusual position. While most anesthetics exert a retarding effect on circulation and metabolism, ketamine clearly has the opposite effect.

Figure 1 shows the synopsis of the most important circulatory characteristics after a representative individual test. All the pressures were recorded in the blood, the HZV was measured by the thermo-dilution method [13] and the the coronary blood supply was measured by means of a Pitot pipe catheter using the method of Bretschneider [8]. As the figure shows, the injection of ketamine in the animal test causes an increase in heart frequency (HF), HZV (lower curve), coronary blood supply (V_{cor}) and the myocardial O₂ consumption, together with a reduction in coronary venous sat-

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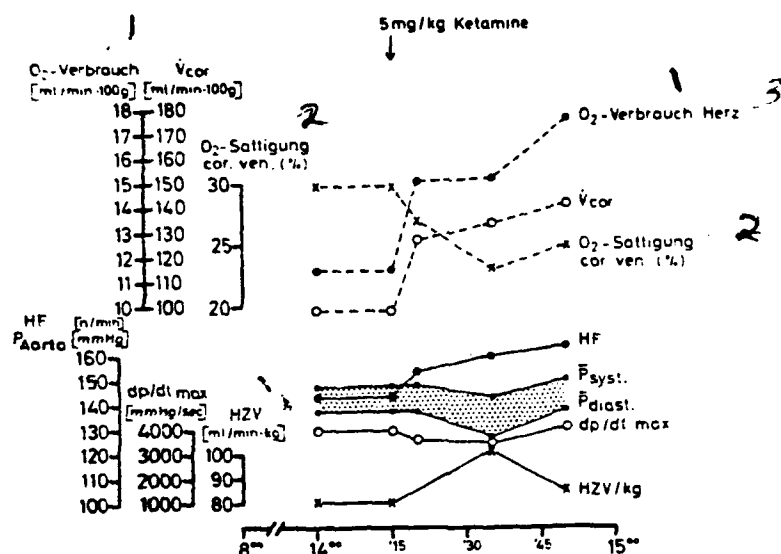


Fig. 1. Effects of ketamine on the coronary venous O₂ saturation (upper curve), the myocardial O₂ consumption (heart O₂ consumption), the coronary blood supply ($\dot{V}_{cor}$), the heart frequency (HF), the systolic and diastolic pressure, the rate of pressure increase in the left ventricle (dp/dt_{max}) and the HZV in an animal test. By Kettler and co-workers (1970)

Key: 1 = consumption, 2 = saturation, 3 = heart

uration (upper falling curve). The pressures and the rate of decrease dp/dt_{max} are obviously higher, and are scarcely still being affected in the case shown, since narcosis had already been maintained for 6 hours when the injection was given. The circulatory behavior shown here is in agreement with the findings of other work groups [1,14,15,17,18]. The pharmacological mechanism that causes this effect has up to now never been explained with complete satisfaction, however. Virtue and co-workers [18] interpreted these circulatory changes in the presence of ketamine as a result of an intravascular release of catecholamine; the circulatory behavior shown in Fig. 1 supports this association entirely. According to the findings of Traber and co-workers [17], however, there does not seem to be a direct or indirect sympathomimetic effect caused by ketamine. This work group found in animal experiments after pre-medication with ganglioplegics (hexamethonium) neither a positive chronotropic

effect nor an increase in blood pressure in the case of ketamine narcosis. If it did exert a sympathomimetic action, ketamine would also have to have the same circulatory effects described above even in the event of ganglia block. Other findings [16] indicate that ketamine possesses anti-cholinergic properties, so that the circulatory reactions found could be explained by a relatively intensified sympathicotonus as a result of a vagus restriction. However, the obviously higher total oxygen consumption compared with other narcotics, that we found in earlier studies [1], cannot be explained by this type of atropine-like effect. The increased O_2 consumption of the entire organism is an indication that a metabolic increase induced by ketamine takes place not only in the cardiovascular system - which in any case only amounts to about 10% of the entire system [3]. A release of catecholamine could not be entirely excluded as a possible cause of this even given the above findings, since to our knowledge there are still no findings available on comparative changes in the catecholamine level during ketamine narcosis. Therefore it seemed to us appropriate to take comparative measurements of the plasma concentrations of catecholamines, glucose and non-esterified fatty acids. In addition, the following study will provide supplementary studies of the pharmacological causes of the increase in the entire metabolism during ketamine narcosis.

Method

Eight mongrel dogs weighing between 19 and 27 kg were pre-medicated with 1 mg of scopolamine and 30 minutes later received intravenously on average 20 mg/kg body weight of ketamine which produced in them a condition similar to narcosis. Before administration of the pre-medication, a blood sample was taken from each animal. The blood sample was not taken until the test animal had calmed down after the cannula insertion and the heart beat was lower than 100/min. After giving ketamine, blood samples were taken at 15 minute intervals and the volume loss in the circulation of the test animal resulting from the withdrawal of blood was compensated for by infusion of synthetic blood. Measurement of catecholamine was carried out simultaneously by two different procedures. The Institute

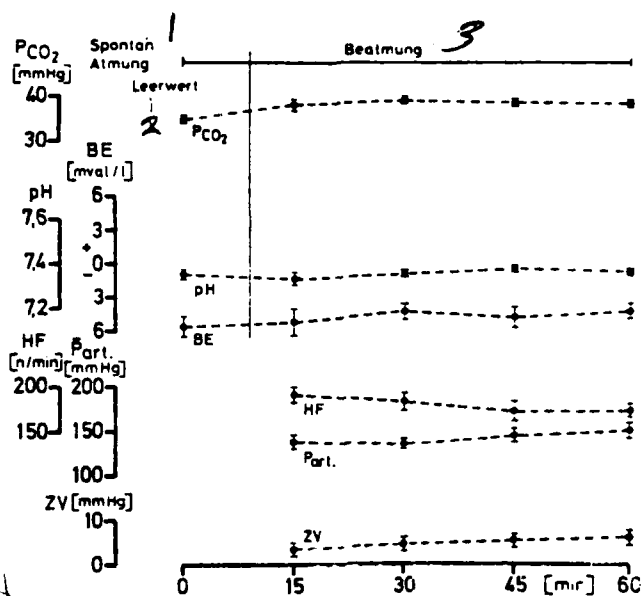


Fig. 2. The behavior of PCO₂, pH base excess and the average arterial pressure, heart beat and the central venous pressure during ketamine narcosis *is discussed.*

Key: 1 = spontaneous respiration, 2 = resting value, 3 = artificial respiration

for Forensic Medicine located here carried out the measurements for us with a modification of the trihydroxylindol (THI) method of Lund, while we ourselves used the procedure given in 1968 by Weil-Malherbe and Bigelow [19]. The free (non-esterified) fatty acids were measured by the method of Duncombe [5], the blood sugar was determined by the enzyme method and the acid base balance by the Astrup method. The blood withdrawal and the pressure measurements were taken through percutaneously inserted steel cannulas or irrigating catheters.

All the animals were intubated after narcosis had been induced and normo-ventilated by means of a URAS (Hartmann & Braun Co.) with a laughing gas/oxygen mixture in a ratio of 80:20% by an Engstrom Respirator, while the expiration CO₂ concentration was checked. By using an oxy-test (Hartmann & Braun Co.) in conjunction with the inspiration breathing tube, the O₂ concentration could be monitored continuously. After the final blood sample had been taken,

a EHN spirometer [6] was introduced into the respiration cycle to measure the oxygen consumption and we waited for a steady state. The narcosis lasted altogether about 1½ hours. After extubation and administration of a broad-spectrum antibiotic, the dogs were returned to the kennel.

Results

To induce narcosis all the animals required a very high dose of ketamine compared with humans: on average 20 mg/kg h of ketamine. After the initial dose had been administered the animals lay down on their sides, their eyes remained open all the time, now and again there was blinking, swallowing and slow movement of the head. The animals showed no pain reaction at all to needles. In most cases subsequent injections of ketamine were required at intervals of 20 minutes. On average the animals needed 20 mg/kg h to maintain narcosis. Stronger counter respiration was considered a sign of a decrease in the depth of the narcosis; this was frequently associated with increased swallowing.

Figure 2 shows a summary of the acid base balance and the most important circulation levels during the first hour of narcosis. From top to bottom, the values are shown for pCO_2 , pH, base excess, heart beat, average arterial pressure and central venous pressure. The bars on the dotted lines indicate the average error in the mean value. The pCO_2 is 35 mm Hg before narcosis and rises with artificial respiration according to the adjusted ventilation level to a value of 38 mm Hg. The pH level at the beginning is 7.35 and is barely affected by narcosis. The base excess rises from a pre-narcosis level of -5.8 mval/l to -4 mval/l.

In the area of the acid base balance, therefore, we see no particular changes during narcosis with ketamine. On the other hand, the heart beat is worth noting: 15 minutes after the administration of ketamine it is on average 180/min and after another 45 minutes it is still 165/min. At the same time the average arterial pressure rises from 137 mm Hg to 150 mm Hg. The central venous pressure (lower curve) remains within the normal range. The average values for the heart beat and the mean arterial pressure are, according to our experiences with other methods of narcosis [10,11], much higher with ketamine.

The values for adrenaline and noradrenaline turned out much less homogeneously in relation to all the other values measured. This is probably the result on the one hand of the not entirely problem-free method of catecholamine measurement; however, on the other hand, measured by the task that falls physiologically to the catecholamines, there is a greater biological scattering range here, even under standardized conditions. The two methods used produced the same quantitative results. The rapid decomposition of these compounds made it necessary to process each individual sample immediately. For each individual determination of the blood values listed above a total of about 40 ml of blood had to be withdrawn. The decrease in the blood sample taken before narcosis is already problematic. The insertion of a cannula certainly places a certain amount of stress on the test animal, although the insertion site on the extensor side of the foreleg was generously infiltrated with a local anesthetic (Lidocain). Some animals reacted with an increase in heart beat, however, in most cases there was a decrease in heart beat with a tendency to arrhythmia. In both instances we waited until a "resting condition" with a heart beat of 90/min had established itself.

The behavior of the plasma balance of free fatty acids, glucose, adrenaline and noradrenaline (Weil-Malherbe method) and the reaction of the heart beat are shown in Fig. 3. In the upper section of Fig. 3 the course of the average plasma balance is shown for noradrenaline. The curve shows a drop from 1.27 μ /l to 0.9 μ /l after 15 minutes with a subsequent rise to 1.5 μ /l after 30 minutes. The 15 minute level of the adrenaline concentration in the plasma rises from its initial level of 0.17 μ /l to 0.48 μ /l and falls after 30 minutes to a final level of 0.33 μ /l. Comparison of the three samples for noradrenaline and adrenaline using the Kruskal-Wallis tests, a parameter-free variance analysis, showed no significant differences for both catecholamines at the 5% level. We must assume, therefore, that the variations in the three samples occurred purely accidentally. The rise in the heart beat shows clearly, however, that the circulatory reactions typical of ketamine had taken place in the area of investigation.

The glucose level drops from its initial level of 78 mg-% only slightly (about 5 mg-%), while the fatty acid level increases slight-

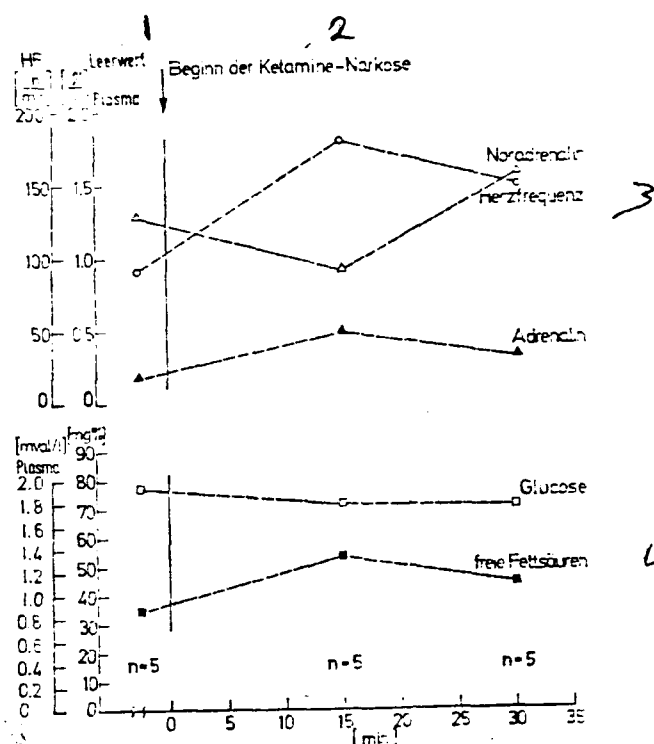


Fig. 3. The change in heart beat and the plasma concentration of noradrenaline, adrenaline, glucose and free fatty acids during ketamine narcosis.

Key: 1 = resting value, 2 = start of ketamine narcosis, 3 = heart beat, 4 = fatty acids

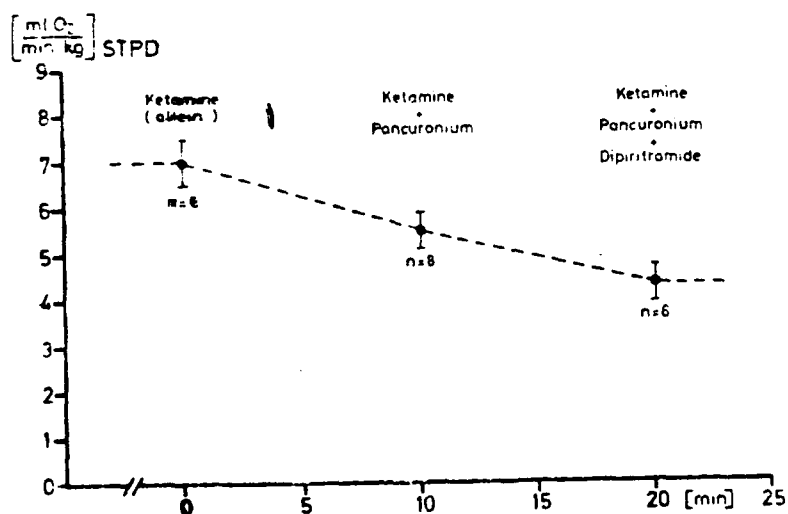


Fig. 4. Oxygen consumption during ketamine narcosis after administration of a muscle relaxant and a morphine derivative.

ly above the normal level (0.09-0.6 mval/l) 15 minutes after administering ketamine. The resting level of the free fatty acids is on average 0.9 mval/l, the level after 15 minutes of ketamine narcosis is 1.3 mval/l and after 30 minutes it is 1.1 mval/l.

After taking the last blood sample, the up to then open system was converted to a closed one and we waited for a steady state. Then the oxygen consumption was measured over a period of 10 minutes. The normal body temperature of the dog is about 38°C rectally. Before and during the ketamine narcosis the temperature in all the dogs remained on average unchanged at 38.6°C. The O₂ consumption levels are given here in ml O₂ (STDP)/min and kg body weight and, based on a Q₁₀ of 1.7, are converted to an animal temperature of 37°C. The mean value standardized in this way, which was obtained from eight test animals, is 7.2 ml O₂/min (Fig. 4). This means that the oxygen consumption during ketamine narcosis is much higher than the O₂ consumption levels that we found recently using other narcosis methods [1]. For the sake of comparison, the O₂ consumption during barbiturate narcosis was 5.1 ml O₂/min·kg, during halothane narcosis it was 4.6 ml O₂/min·kg and it was lowest during methoxyflurane narcosis at 3.9 ml O₂/min·kg. Following the measurements during ketamine narcosis, the animals were injected with a muscle relaxant (0.1 mg/kg body weight Pancuronium). The average O₂ consumption fell 10 minutes later to 5.5 ml O₂/min·kg, or by about 30% (Fig. 4). Administration of a morphine derivative produced a further drop in O₂ consumption. 10 minutes after injection of 1 mg/kg of dipiritramide the average O₂ consumption was 4.3 ml O₂/min·kg or 60% of the initial value (Fig. 4).

Discussion of the results

The rise in pressure and heart beat that occurred during ketamine narcosis and the increases in the entire system indicate a release of catecholamine as the common cause of these side-effects. Among the catecholamines, adrenaline in particular possesses the effect of increasing the metabolism as well as having an effect on the circulation. Noradrenaline has a similar qualitative effect in this respect, however to a lesser extent. The O₂ consumption of 7.2 ml O₂/min kg measured during ketamine narcosis is obviously higher

than the average O_2 consumption during other narcosis procedures and when dogs are at rest and awake. In the latter case, according to the findings of the work group Brendel and co-workers [2], it is on average 5.7 ml O_2 /min·kg and thus is on the order of magnitude of the O_2 consumption levels that are found under narcosis conditions (halothane, NLA, barbiturate) [1]. The increase in O_2 consumption during ketamine narcosis by about 25% above the normal level at rest can be rapidly eliminated by administering a depolarization-suppressing muscle relaxant (cf. Fig. 4). It transpires, therefore, that almost the entire increased rate of O_2 consumption during ketamine narcosis can be attributed to increased muscle tone which is probably caused by the central nervous system [15]. Thus the catecholamines can be eliminated as the cause, at least relative to the increase in metabolism that has been described, since the circulatory changes discussed above are largely still present after administration of the muscle relaxant.

When the measurements of the catecholamine levels in the plasma are compared, the fluctuations in their curves show that the average levels of the individual samples demonstrate deviations of varying degrees of magnitude. The resulting differences are not statistically significant, however. Even indirectly by means of measuring the glucose level in the blood, no indication could be found of any release of large amounts of catecholamines. When adrenaline and noradrenaline pour out of the medulla of the suprarenal gland, glycogenolysis is stimulated in the skeletal muscle, the fatty tissue and the liver. The activation of glycogenolysis, especially in the liver, would then have to produce an obvious increase in the glucose level in the blood. However, the glucose concentration remains essentially unchanged within the time period of the study, as can be seen in Fig. 3. The free fatty acids, on the other hand, increase by 40% 15 minutes after administration of ketamine and 20 minutes later are about 20% higher than the level at rest. The increased release of fatty acids by lipolysis from the fatty tissue is caused among other things by increased catecholamine activity. It can be concluded from the behavior of the fatty acids - if one looks at it together with the circulatory reaction - that the introduction of ketamine narcosis induces a more intense sympathotonic condition in the test animals. According to studies

by Feigelson et al. [7], the fatty acid level does in fact increase with infusions of noradrenaline up to 8 times the level at rest. The increase in the fatty acid level found here therefore has no particular significance. Possibly, however, the loss of the resting level or the introduction of narcosis produces a greater "stress factor" to which the organism responds with the typically delayed increase in free fatty acids [12]. The descending trend in the fatty acid curve from the 15 minute level to the 30 minute level would support this association.

The findings reported here, like those of Traber et al. [17], dispute a direct or indirect sympathomimetic action on the part of ketamine. Accordingly, the anti-cholinergic effect detected by Seifen and Mahmel [16] appears to be the most likely explanation for the increased sympathotonus. The idea of a pharmacological mechanism of this kind is supported also by the recent report by Kettler et al. [11] of the great catecholamine sensitivity of the myocardium and the circulation in the presence of ketamine, compared with other narcotics.

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